

WHAT IS CLAIMED IS:

1 1. An isolated nucleic acid encoding an IRAK-4 polypeptide, said
2 polypeptide having at least about 98% amino acid sequence identity to SEQ ID NO:1 or
3 to a subsequence thereof, wherein the amino acid sequence of the polypeptide comprises
4 an alanine residue at an amino acid position corresponding to amino acid position 81 of
5 SEQ ID NO:1, and wherein said nucleic acid comprises at least about 400 nucleotides.

1 2. The nucleic acid of claim 1, wherein the polypeptide further
2 comprises an amino acid selected from the group consisting of:

- 3 (i) a valine residue at an amino acid position corresponding to amino acid
4 position 432 of SEQ ID NO:1;
- 5 (ii) a leucine residue at an amino acid position corresponding to amino
6 acid position 437 of SEQ ID NO:1;
- 7 (iii) an arginine residue at an amino acid position corresponding to amino
8 acid position 444 of SEQ ID NO:1; and
- 9 (iv) a glutamine residue at an amino acid position corresponding to amino
10 acid position 451 of SEQ ID NO:1.

1 3. The nucleic acid of claim 2, wherein the polypeptide comprises
2 each of the amino acids listed as (i) to (iv).

1 4. The nucleic acid of claim 1, wherein the polypeptide comprises an
2 amino acid sequence of SEQ ID NO:1.

1 5. The nucleic acid of claim 1, wherein the polypeptide comprises at
2 least about 100 amino acids.

1 6. The nucleic acid of claim 1, wherein the polypeptide comprises at
2 least about 450 amino acids.

1 7. The nucleic acid of claim 1, wherein the nucleic acid comprises a
2 cytosine at a nucleotide position corresponding to nucleotide position 242 of SEQ ID
3 NO:2.

1 8. The nucleic acid of claim 7, wherein the nucleic acid further
2 comprises a nucleotide selected from the group consisting of:

1 9. The nucleic acid of claim 8, wherein the nucleic acid comprises
2 each of the nucleotides listed as (i) to (v).

1 10. The nucleic acid of claim 1, wherein the nucleic acid comprises a
2 nucleotide sequence of SEQ ID NO:2.

1 11. The nucleic acid of claim 1, wherein the nucleic acid comprises at
2 least about 1350 nucleotides.

1 12. The nucleic acid of claim 1, wherein the polypeptide specifically
2 binds to antibodies generated against a polypeptide comprising an amino acid sequence of
3 SEQ ID NO:1.

1 13. The nucleic acid of claim 1, wherein the nucleic acid is operably
2 linked to a promoter.

1 14. An expression cassette comprising the nucleic acid of claim 13.

1 15. An isolated cell comprising the expression cassette of claim 14.

1 A6. An isolated IRAK-4 polypeptide, said polypeptide having at least
2 about 98% amino acid sequence identity to SEQ ID NO:1 or to a subsequence thereof,
3 wherein the amino acid sequence of the polypeptide comprises an alanine residue at an
4 amino acid position corresponding to amino acid position 81 of SEQ ID NO:1, and
5 wherein the polypeptide comprises at least about 100 amino acids.

1 17. The polypeptide of claim 16, wherein the polypeptide further
2 comprises an amino acid selected from the group consisting of:
3 (i) a valine residue at an amino acid position corresponding to amino acid
4 position 432 of SEQ ID NO:1;
5 (ii) a leucine residue at an amino acid position corresponding to amino
6 acid position 437 of SEQ ID NO:1;
7 (iii) an arginine residue at an amino acid position corresponding to amino
8 acid position 444 of SEQ ID NO:1; and
9 (iv) a glutamine residue at an amino acid position corresponding to amino
10 acid position 451 of SEQ ID NO:1.

1 18. The polypeptide of claim 17, wherein the polypeptide comprises all
2 of the amino acids listed as (i) to (iv).

1 19. The polypeptide of claim 16, wherein the polypeptide comprises an
2 amino acid sequence of SEQ ID NO:1.

1 20. The polypeptide of claim 16, wherein the polypeptide is encoded
2 by a nucleic acid comprising a nucleotide sequence of SEQ ID NO:2.

1 21. The polypeptide of claim 16, wherein the polypeptide specifically
2 binds to antibodies generated against a polypeptide comprising an amino acid sequence of
3 SEQ ID NO:1.

1 22. The polypeptide of claim 16, wherein the polypeptide comprises at
2 least about 450 amino acids.

1 23. An isolated nucleic acid encoding an IRAK-4 polypeptide, said
2 polypeptide comprising at least about 70% amino acid sequence identity to SEQ ID NO:3
3 or to a subsequence thereof.

1 24. The nucleic acid of claim 23, wherein said polypeptide comprises
2 an amino acid sequence of SEQ ID NO:3.

1 25. The nucleic acid of claim 23, wherein said nucleic acid comprises
2 at least about 70% nucleotide sequence identity to SEQ ID NO:4 or to a subsequence
3 thereof.

1 26. The nucleic acid of claim 23, wherein said nucleic acid comprises a
2 nucleotide sequence of SEQ ID NO:4.

1 27. The nucleic acid of claim 23, wherein said nucleic acid hybridizes
2 under stringent hybridization conditions to a nucleic acid comprising a nucleotide
3 sequence of SEQ ID NO:4.

1 28. The nucleic acid of claim 23, wherein said nucleic acid is operably
2 linked to a promoter.

1 29. An expression cassette comprising the nucleic acid of claim 28.

1 30. An isolated cell comprising the expression cassette of claim 29.

[Signature]
2 31. A method of making an IRAK-4 polypeptide, the method
comprising:
3 (i) introducing a nucleic acid of claim 1 or claim 19 into a host cell or
4 cellular extract;
5 (ii) incubating said host cell or cellular extract under conditions such that
6 said IRAK-4 polypeptide is expressed in the host cell or cellular extract; and
7 (iii) recovering the IRAK-4 polypeptide from the host cell or cellular
8 extract.

1 32. A method of identifying a compound useful in the treatment of
2 inflammatory diseases, comprising the steps of:

3 (i) contacting an IRAK-4 polypeptide with said compound, wherein said
4 IRAK-4 polypeptide comprises at least about 70% amino acid sequence identity to SEQ
5 ID NO:1 or SEQ ID NO:3; and
6 (ii) determining the functional effect of said compound on said IRAK-4
7 polypeptide.

1 33. The method of claim 32, wherein said IRAK-4 comprises an amino
2 acid sequence shown as SEQ ID NO:1 or SEQ ID NO:3.

1 34. The method of claim 32, wherein the compound inhibits IRAK-4
2 kinase activity.

1 35. The method of claim 32, wherein said IRAK-4 is present inside of
2 a eukaryotic cell.

1 36. A method of treating an inflammatory disease in a patient, the
2 method comprising administering to said patient a therapeutically effective amount of a
3 compound that modulates IRAK-4.

1 37. The method of claim 36, wherein said compound inhibits IRAK-4
2 kinase activity.

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1 38. The method of claim 36, wherein said compound is identified using
2 the method of claim 32.

1 39. The method of claim 36, wherein the inflammatory disease is
2 selected from the group consisting of pulmonary diseases and diseases of the airway,
3 transplant rejection, autoimmune diseases, cancer, cardiovascular diseases, diseases of the
4 central nervous system, CD14 mediated sepsis, non-CD14 mediated sepsis, osteoarthritis,
5 osteoporosis, psoriasis, diseases of the skin, inflammatory bowel disease, Behcet's
6 syndrome, ankylosing spondylitis, sarcoidosis, gout, and ophthalmic diseases and
7 conditions.

1 40. The method of claim 39, wherein the pulmonary disease and
2 disease of the airway is selected from the group consisting of Adult Respiratory Disease
3 Syndrome (ARDS), Chronic Obstructive Pulmonary Disease (COPD), pulmonary fibrosis,
4 interstitial lung disease, asthma, chronic cough, and allergic rhinitis..

1 41. The method of claim 39, wherein the autoimmune disease is
2 selected from the group consisting of rheumatoid arthritis, systemic lupus erythematosus,
3 multiple sclerosis, and diabetes.

1 42. The method of claim 39, wherein the cancer is selected from the
2 group consisting of solid tumors, skin cancer, and lymphoma.

1 43. The method of claim 39, wherein the cardiovascular disease is
2 selected from the group consisting of stroke and atherosclerosis.

1 44. The method of claim 39, wherein the disease of the central nervous
2 system is a neurodegenerative disease.

1 45. The method of claim 39, wherein the disease of the skin is selected
2 from the group consisting of rash, contact dermatitis, and atopic dermatitis.

1 46. The method of claim 39, wherein the inflammatory bowel disease
2 is selected from the group consisting of Crohn's disease and ulcerative colitis.

1 47. A method of inhibiting the transduction of a signal resulting from
2 the activation of an IL-1R/Toll receptor in a cell, the method comprising introducing into
3 said cell an inhibitor of the activity or expression of IRAK-4.

1 48. The method of claim 47, wherein said IL-1R/Toll receptor is
2 activated by IL-1.

1 49. The method of claim 47, wherein said inhibitor comprises a
2 dominant negative form of IRAK-4.

1 50. The method of claim 49, wherein said dominant negative form of
2 IRAK-4 comprises a mutation in a lysine residue in the ATP binding pocket.

1 51. The method of claim 50, wherein said mutation comprises a
2 substitution of alanine residues for lysine residues within said IRAK-4 at amino acid
3 positions corresponding to positions 213 and 214 of SEQ ID NO:1.

1 52. The method of claim 49, wherein said dominant negative form of
2 IRAK-4 is a truncated form of IRAK-4.

1 53. The method of claim 52, wherein said truncated form of IRAK-4
2 consists essentially of amino acids 1 to 191 of SEQ ID NO:1.

~~1~~ 54. The method of claim 47, wherein said inhibitor comprises a
~~2~~ compound identified using the method of claim 32.

~~1~~ 55. The method of claim 45, wherein said inhibitor inhibits activation
~~2~~ of at least one transcription factor.

~~1~~ 56. The method of claim 53, wherein said transcription factor activates
~~2~~ NF κ B in said cell.

~~1~~ 57. A nonhuman transgenic animal comprising a mutation in an
~~2~~ endogenous IRAK-4 gene.

~~1~~ 58. The transgenic animal of claim 57, wherein said mutation
~~2~~ inactivates said endogenous IRAK-4 gene.

~~1~~ 59. The mutation of claim 58, wherein said mutation comprises a
~~2~~ deletion of all or part of said endogenous IRAK-4 gene.

~~1~~ 60. The transgenic animal of claim 57, wherein said animal is a mouse.

~~1~~ 61. An isolated mutant mammalian cell comprising a mutation in an
~~2~~ endogenous IRAK-4 gene.

~~1~~ 62. The isolated mutant mammalian cell of claim 61, wherein said
~~2~~ mutation inactivates said endogenous IRAK-4 gene.

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